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10/659,519	09/09/2003	David Sidransky	JHU1300-6	6054

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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 09/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/659,519	SIDRANSKY ET AL.
	Examiner	Art Unit
	Katherine Salmon	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-24* is/are pending in the application.

4a) Of the above claim(s) *20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152. .

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/09/2003*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group 1, Claims 12-19 in the reply filed on 6/15/2006 is acknowledged.

2. Claims 12-24 are pending. Claims 1-11 are canceled. Claims 20-24 are withdrawn from consideration as being drawn to a nonelected invention.

3. An action on the merits for Claims 12-19 is set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 12-19 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: steps required to detect methylation. The claims merely require analysis of amplified products, but there is no nexus between the analysis and methylation in last line such that analysis would determine methylation. The lack of such a nexus amounts to a gap between the steps.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 16-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

<u>The nature of the invention and breadth of claims</u>

Claim 16 is drawn to a method wherein methylation of the p16 gene is indicative of a neoplasm. Claim 17 defines the neoplasm.

The claims are broadly drawn to detecting methylation in ANY neoplasm.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts the prior art has shown abnormalities of p16 gene in primary tumors of certain cancers (p. 3 lines 3-5). The specification asserts in eukaryotic cells methylation of cytosine residues immediately 5' to a guanosine occurs predominantly in CG poor regions (p. 3 lines 18-19). The specification asserts discrete regions of CG dinucleotides (CpG islands) are unmethylated in normal cells and methylation of the 5' regulatory regions lead to transcriptional repression (p. 3 lines 22-23).

The specification asserts a method for detection of a cell proliferative disorder (neoplasm) comprising contacting a target tissue to detect alterations in p16 wherein alterations utilize a methylation sensitive restriction endonuclease to detect p16 methylation (p. 6 lines 3-7).

The specification asserts methylated cell lines express an abundant, shortened p16 transcript devoid of exon 1 coding sequence (p. 9 last paragraph). The specification asserts hypermethylation of the 5'CpG island of p16 is frequent in cell lines and primary tumors of common human neoplasms (p. 10 1st paragraph). The specification asserts DNA methylation can occur in neoplasms with homozygous deletion (breast, renal) and those not associated with loss of p16 (colon and prostate) (p. 10 1st paragraph). The specification asserts hypermethylation in the p16 promoter region is a common abnormality of p16 in human cancers (p. 10 1st paragraph).

The specification asserts detection of methylation of 5'CpG p16 DNA is done by isolating DNA from sample tissue followed by amplification (p. 42 last paragraph). The

specification teaches the DNA is subjected to restriction endonuclease analysis using methylation sensitive enzyme alone or in combination to produce a restriction map (p. 42 last paragraph). The specification assert methylation at a site on the DNA is recognized and cleaved by the methylation sensitive enzyme and a unique pattern of DNA fragments is produced depending on the presence or extent of methylation (p. 42 last paragraph).

Working Examples

Example 1 part 1: The specification asserts cells from head and neck cancer cell lines, lung cancer cell lines, pancreatic adenocarcinomas cell lines were extracted (p. 47 last paragraph).

Example 1 part 2 and 3: The specification asserts fragments of exon 1, 2, and 3 were amplified (p. 48 and 49).

Example 6: The specification asserts the 5' CpG island of p16 was analyzed for changes in DNA methylation (p. 59 1st full paragraph). The specification asserts the methylation differences of different restriction sites inside and outside the CpG island (p. 59 1st full paragraph). Table 1 presents 5' CpG island methylation related to allelic status and sequence analysis of the p16 in the cell lines. It is unclear what the table is indicating. The expression of the primary human cancers has not been completed (p. 61) therefore there is no association between primary human cancer and expression of methylation. Further the p16 sequence indicates the majority of the primary human cancers have the wild-type p16 sequence (p. 61). This indicates p16 with exon 1 present (wildtype) would be observed in primary human cancers, therefore it is

unpredictable to make an association of a mutant p16 gene (absent of exon 1) with cancers.

Example 7: The specification asserts sequence analysis of exons 1 and 2 of p16 in cell lines showed only one mutation in a HNSCC cell line (p. 62 2nd paragraph). The specification asserts the mutation caused exclusion of exon 2 but the line contained an unmethylated 5' CpG island since methylation and point mutation are independent modes of gene inactivation (p. 62 2nd paragraph).

Example 10: The specification asserts detecting de novo methylation of p16 in tumor cells (p. 65 last paragraph). The specification asserts 4 NSCLC show de novo methylation whereas one does not exhibit methylation (p. 66 Figure 6b). The specification asserts 7 of 25 NSCLC showed aberrant methylation of p16 whereas 21 control samples did not show detectable methylation (no p value provided) (p. 66 last paragraph). The specification asserts protected CpG sites can be attributed to tumor DNA since normal tissue is not methylated (p. 67 1st paragraph). This is unpredictable because the specification fails to show a significant association of the methylation site of p16 and any tumor cell. It is unclear if 7 or 25 tumor cells would be statistically significant correlation of neoplasm to detection of methylation.

Example 11: The specification asserts Exon 1 of p16 lies in a CpG island which is unmethylated in normal tissue (p. 67 1st full paragraph). The specification asserts restriction with a nonmethylation sensitive restriction enzyme provides a determination of methylation status (p. 67 1st full paragraph). Table 2 shows inactivation of p16 in cell lines and primary tumors (p. 69). The specification asserts a correlation of methylation

to cancer. There is no p value for the number of cell lines or tumors which had a methylated p16 region so it is unclear if there is a correlation. For example the 6 colon adenoma tumors tested only 1 was methylated. Therefore, it is unpredictable to correlate any tumor with methylation. Further, the specification asserts some primary colon cancers had hypermethylated p16 alleles while others had unmethylated alleles (p. 70 1st paragraph last sentence). It is unpredictable to detect ANY neoplasm by detection of methylation. The specification shows some tumor cell lines association with increased methylation and other tumors (colon adenoma) where the association is not clear.

<u>The unpredictability of the art and the state of the prior art</u>

The current art teaches detection of methylation is indicative of not only neoplasm but also aging of normal cells. Yates et al. (Oncogene 2006 Vol 25 p. 1984) teaches that methylation increases with age and malignancy (abstract). Yates et al. teaches that methylation was detected in urine DNA from patients with and without bladder cancer (Abstract). Yates et al. teaches aberrant methylation is not cancer specific and can be found in a normal ageing cell population (p. 1985 1st column 1st paragraph). Yates et al. teaches the overall knowledge of the molecular mechanisms of DNA methylation in health and cancer remains poor and one uncertainty is the extent of aberrant DNA methylation in nonmalignant tissue and the association between ageing and aberrant DNA methylation (p. 1985 last paragraph).

Quantity of Experimentation

The quantity of experimentation in this area would be extremely large since there is significant number of parameters that would have to be studied. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine the correlative association of every possible neoplasm and detection of methylation.

The skilled artisan would need to perform undue experimentation to determine if detection of methylation by amplification of p16 gene is indicative of ANY neoplasm.

To use the invention as presented would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus the applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the claimed method of detecting ANY neoplasm. The skilled artisan would have to perform undue experimentation to determine the relationship of NAY neoplasm and detection of methylation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the negative teachings in the art, and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 12-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Herbert et al. (Blood December 1994 Vol. 84 p. 4038).

With regard to Claim 12, it is unclear if there are any steps between detecting amplification and detecting methylation, therefore, a method teaching primer amplification of the exon 1 and 2 region followed by analysis of the amplified product of the p16 gene would encompass all the limitations of the claim. Herbert et al. teaches exon 1 and 2 were amplified by PCR and analyzed (p. 4039 1st column 1st full paragraph). Herbert et al. teaches the analysis using Southern blot deletion of the MTS1 was detected (p. 4039 2nd column 1st full paragraph). Herbert et al. teaches a Southern blot approach to detect deletions in the MTS1 gene (p16 gene) (Abstract). Therefore, Herbert et al. teaches amplifying exon 1 and 2 and detecting deletions of exon 1. Herbert et al. teaches the MTS1 gene is also known as P16 (p. 4038 1st column last sentence).

With regard to Claim 13, the instant specification teaches the 5'ALT region is 5' to exon 2 of P16 (MTS1) gene (p. 5 lines 6-9). Herbert et al. teaches primers to amplify exon 2 (p. 4039 1st column 1st full paragraph). The 3' primer used to amplify exon 2 could be used to amplify the region upstream (5') to exon 2 (5'ALT), therefore, Herbert et al. teaches primers that "permit" amplification of 5'ALT.

With regard to Claim 14, Hebert et al. teaches detection of deletions of MTS1 in 55 acute lymphoblastic leukemia patients (Abstract). With regard to Claim 15, Hebert et al. teaches detection in peripheral blood (fluid) (p. 4038 2nd column Materials and Methods). With regard to Claim 16, Hebert et al. teaches a method of detecting deletions in leukemia samples (neoplasm).

7. Claims 12, and 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Tulchinsky et al. (Proc. National Academy Science 1992 Vol. 89 p. 9146).

With regard to Claim 12, Tulchinsky et al. teaches amplifying the Mts1 gene in a plasmid (p. 9147 1st column Plasmid Construction). Tulchinsky et al. teaches the mts1 (p16 gene) gene is specifically expressed in certain metastatic tumors (Abstract). Tulchinsky et al. teaches a role of methylation in progression of the nonmetastatic CSML-1 adenosarcoma cell line toward the metastatic CSML-100 adenosarcoma cell line (abstract). Tulchinsky et al. teaches analysis was preformed on the amplified MTS1 fragment to determine methylation interference (p. 9147 2nd column In Vitro Foot printing). Tulchinsky et al teaches determining methylation based on amplified product analysis (p. 9147 2nd column In Vitro Foot printing). The plasmid contains the first exon,

the first intron, and the nontranslated part of the second exon (p. 9147 1st Column Plasmid Construction).

Tulchinsky et al teaches detecting methylation interference (p. 9147 1st column last sentence). With regard to Claim 15, Tulchinsky et al. teaches using cells from a mouse adenosarcoma cell (p. 9147 1st column Cell lines). With regard to Claim 16, Tulchinsky et al. teaches the progression of the CSML-0 cell line (non-tumor) toward CSML-100 (metastatic, neoplasm) cause an inactivation of the normal methylation system resulting in hypomethylation of the mts1 gene (p. 9150 1st column 1st full paragraph). With regard to Claim 17, Tulchinsky et al. teaches detection in adenosarcoma cells (abstract).

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Katherine Salmon
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